## REMARKS

The applicants appreciate the Examiner's thorough examination of the application and request reexamination and reconsideration of the application in view of the preceding amendments and the following remarks.

The Examiner rejects claims 1 and 4-14 under 35 U.S.C. §103(a) as being unpatentable over *Willner et al.* WO 98/40739 in view of U.S. Pat. No. 4,889,992 to *Hoberman* and U.S. Pat. No. 5,372,936 to *Fraatz et al.*

As discussed more fully below, the cited references do not teach or suggest the applicants' claimed combination including an electrical connection between the sealed in bio-sensor and the detection circuit, in contrast to the applicants' independent claim 1 as amended.

Also as discussed more fully below, one skilled in the art at the time of the applicants' invention would not have combined the cited references because, *inter alia*, the structure and principles of the primary reference *Willner et al.* (as well as the *Karube* reference) and the secondary references *Hoberman* and *Fraatz et al.* are diametrically opposite one another.

### The Cited References Do Not Disclose, Teach Or Suggest The Applicants' Claimed Combination Including An Electrical Connection Between The Sealed-In Bio-Sensor And The Detection Circuit

*Willner et al.* does not disclose that the bio-sensor is sealed within the vessel. Although *Willner et al.* teaches a bio-sensor for cells that includes an electrical connection, it is in sharp contrast to the secondary references *Hoberman* and *Kraatz et al.*, which teach away from an electrical connection.

In contrast to *Willner et al.*, *Hoberman* teaches away from an electrical connection

between the detector and the baffle insert 36 within the sealed vessel and the detector 58. See, e.g. Fig. 6 of *Willner et al.* The test vials of *Hoberman* pass (on a conveyor belt) between an infrared source and an infrared detector, and the infrared radiation transmitted is detected. See, e.g. *Hoberman* column 6, lines 30-50. There is no electrical connection between the baffle insert and the detector. Among other things, *Hoberman*'s conveyor system would be defeated if such an electrical connection were introduced.

*Fraatz et al.* teaches away from an electrical connection by teaching an optical coupling between between optodes in the container and the excitation and detection assembly. A light waveguide transmits excitation radiation towards the optodes while receiving the optical radiation emitted. One arm of the waveguide is coupled to the detector 11. See, e.g. *Fraatz et al.* column 11, line 60 through column 12, line 7. In Fig. 3 of *Fraatz et al.* the principle is the same, but there is a probe 10 between the two-armed light waveguide 10 and the optode 3 to permit measurements to be taken in the gas space 6 and the culture medium 5. In either event, however, there is no electrical connection between the optodes and the waveguide that leads to the detector.

The applicants further note that *Willner et al.* is not properly combinable with either *Hoberman* or *Kraatz et al.* for reasons that are more fully set forth below.

With respect to the *Karube* reference (cited by the Examiner for another purpose), it teaches a device and method for analysis of biochemicals that includes electrodes connected to an oscillator circuit by wires. *Karube* does not teach a sealed vessel. In fact, the device and method taught by *Karube* teach away from use of a sealed vessel.

*Karube* teaches flow type cells into which various solutions are eluted and replaced with other solutions. Liquid circulation, including pumps, inlet and outlet pipes, and valves are also

taught by *Karube*. Thus, if *Karube*'s bio-sensor was in a sealed vessel, the device and method taught by *Karube* would not work. Therefore, *Karube* is not properly combinable with *Hoberman* or *Fraatz et al.*, which each teach a sealed vessel. Also, *Karube* teaches away from the applicants' claimed invention which includes a bio-sensor sealed in the vessel in the culture medium with the sample.

Consequently, the applicants' claimed combination is not taught or suggested by the cited references. Accordingly, independent claim 1, as well as claims 2-17 that depend directly or indirectly from claim 1, are in condition for allowance.

The *Willner et al.* Primary Reference Is Not Properly Combinable With the Secondary References *Hoberman* And *Fraatz et al.* Because They Teach Away From One Another

The applicants submit that the secondary references *Hoberman* and *Fraatz et al.* teach away from the primary reference *Willner et al.*, and thus the references are not properly combinable.

*Willner et al.* and *Hoberman*

*Willner et al.* teaches a system for assaying cells in a liquid medium utilizing a piezoelectric crystal-based sensing member having one or more metal plates on its surface. *Willner et al.* further teaches contacting the sensing member with the specimen in the liquid medium. See, e.g. *Willner et al.* at page 5, line 20 through page 6, line 4 and page 6, lines 22-24.

In sharp contrast, *Hoberman* does not teach a sensor or contact with the medium. Instead, *Hoberman* teaches an instrument for the detection of microorganisms in a culture media by means of the measurement of gaseous products generated during bacterial metabolism. A special

vial containing a gas-liquid separation system permits measurement through the walls of the vial by determination of the infrared radiation absorption by the gaseous contents within the vessel. See, e.g., *Hoberman*'s Abstract.

Also, *Willner et al.* teaches that on the surface of the metal plates are specific binding entities which bind to an epitope on cells to be assayed, thus changing the mass of the sensing member and in turn the resonance frequency of the sensing member which is measured. See, e.g. *Willner et al.* at page 5, line 20 through page 6, line 4 and page 6, lines 22-24.

In contrast, *Hoberman* teaches that for measurement to take place, the vial must pass between an IR source and a detector. See, e.g., Figs. 5 and 6 of *Hoberman*, and column 6, lines 30-54. *Hoberman* does not teach, *inter alia*, binding entities or changes to a sensing member as a basis for measurement.

Additionally, *Willner et al.* teaches a second aspect of the invention where sensitivity increasing agents are utilized. In this regard, at page 12, lines 1-5, *Willner et al.* states that:

> In accordance with this embodiment of the invention, after contact of the sensing member with said specimen, the sensing member is contacted with said sensitivity increasing agents which once bound to the cells increase the immobilized mass on the surface of the sensing member and hence increases [sic] the change in the resonance frequency.

The applicants recognize the Examiner's point that *Willner et al.* does not require the use of sensitivity increasing agents. However, it is clear that *Willner et al.* does not teach a sealed container, but does teach an embodiment for sequential contact of the sensing member with the specimen first, and then after such contact, contact with a sensitivity increasing agent. Alternatively, *Willner et al.* teaches that where the concentration of more than one type of cell is sought, the specimen is first contacted with the sensing member, then the sensing member is

contacted with a first cell-specific agent. Thereafter, to verify the existence of a second type of cell, a second cell-specific binding agent is then contacted with the sensing member. See *Willner et al.* page 12, lines 11-27.

The latter teachings of *Willner et al.* suggest a non-sealed container. The applicants submit that the teachings of *Willner et al.* suggest that the use a sealed container is precluded because a sealed container would not allow first contact with the specimen, then after such contact, contact with a sensitivity increasing or other type of agent. This is in contrast to the teachings of *Hoberman*, where gas concentration measurements may be adversely effected if the container is not sealed.

*Willner et al.* and *Fraatz et al.*

As noted above, *Willner et al.* teaches a system including a sensor with binding entities, and the sensor is contacted with a liquid medium. When the binding entities bind with an epitope on cells to be assayed, the mass of the sensing member is changed and thereby measurements can be taken.

In sharp contrast, *Fraatz et al.* teaches a liquid indicator that itself changes optical characteristics when chemical changes in the medium occur (which are brought about by the presence of microorganisms in the sample). Inert fluorophores in optodes measure the modulation of the flourescent output caused by changes in the indicator medium. The optodes are optically coupled to an excitation and detection assembly. Radiation emitted by the flourescent component of the sensor is measured, with a change in flourescence (caused by the chemical changes in the liquid indicator medium) indicating the presence of microorganisms. See *Fraatz et al.* Abstract and column 3, lines 22-29 and 44-56.

Additionally, as noted above, it is clear that *Willner et al.* does not teach a sealed container. However, *Willner et al.* does teach an embodiment for sequential contact of the sensing member with the specimen first, and then after such contact, contact with a sensitivity increasing agent, the latter teaching suggesting a non-sealed container. Also as noted, *Willner et al.* teaches that where the concentration of more than one type of cell is sought, the specimen is first contacted with the sensing member, then the sensing member is contacted with a first cell-specific agent. Thereafter, to verify the existence of a second type of cell, a second cell-specific binding agent is then contacted with the sensing member.

Also as noted above, the applicants submit that the teachings of *Willner et al.* suggest that the use a sealed container is precluded because a sealed container would not allow first contact with the specimen, then after such contact, contact with a sensitivity increasing agent (or a cell specific agent). This is in contrast to the teachings of *Fraatz et al.*, where a change in optical quality may adversely effect the measurement if the container is not sealed.

The applicants submit that it is not proper to ignore the specific teachings of cited references in order to find motivation to combine.

> One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. See In re Fine, *id.* at 1600 (Fed. Cir. 1988).

Because the cited references are antithetical to one another, the novel and non-obvious nature of the applicants' claimed invention is evident.

The Cited References Teach Away From The Applicants' Invention

The applicants submit that the cited references teach away from the applicants' claimed

invention, and are all in stark contrast to the applicants' claimed invention.

*Willner et al.* does not teach a sealed container and the embodiments taught by *Willner et al.* as discussed above suggest a non-sealable container.

*Hoberman* teaches an instrument for the detection of microorganisms in a culture medium by means of the measurement of gaseous products generated during bacterial metabolism, and takes measurements through the walls of the vial by determining the infrared radiation absorption by the gaseous contents within the vessel.

*Fraatz et al.* teaches a liquid indicator that itself changes optical characteristics when chemical changes in the medium occur. Inert fluorophores in optodes, optically coupled to an excitation and detection assembly, measure the modulation of the flourescent output caused by changes in the indicator medium, and radiation emitted by the flourescent component of the sensor is measured.

*Karube* teaches flow type cells into which various solutions are eluted and replaced with other solutions. Liquid circulation, including pumps, inlet and outlet pipes, and valves are also taught by *Karube.*

In contrast, the applicants' independent claim 1 recites a smart culture vessel for holding a sample to be tested in a culture medium. The smart culture vessel includes a bio-sensor sealed in the vessel in the culture medium with the sample. The bio-sensor has a coating for attracting at least one pathogen expected in the sample. A detection circuit is configured to drive the bio-sensor at a predetermined frequency and is responsive to the bio-sensor for indicating the presence of a pathogen on the bio-sensor. An electrical connection between the bio-sensor and the detection circuit links the bio-sensor to the detection circuit.

The applicants' invention offers an improvement over known systems by providing

speed, accuracy, safety and convenience, the combination of which was previously lacking.

In summary, the applicants' independent claim 1 is not taught or suggested by the cited references. Accordingly, claim 1 is in condition for allowance. Claims 2-14 depend directly or indirectly from claim 1 claimed by the applicants and thus are also in condition for allowance.

The Examiner further rejects claims 2 and 3 under 35 U.S.C. §103(a) as being unpatentable over *Willner et al.* in view of *Hoberman* and *Fraatz et al.* and further in view of European Pat. No. EP0215669 to *Karube et al.*

Claims 2 and 3 depend directly or indirectly from claim 1, and thus are allowable for at least the foregoing reasons. Additionally, the applicants further note that European Pat. No. EP0215669 to *Karube et al.* discloses a flow cell into which various fluids are drawn including liquid, blood samples, phosphate buffers, and/or removal agents. See, e.g., the *Karube et al.* Abstract and page 4, line 64 through page 5, line 20. This is in contrast to the teachings of *Hoberman* and *Fraatz et al.*, as discussed more fully above.

Finally, the applicant notes that claims 4, 7 and 11-14 have been amended to clearly identify structure. New claims 15-17 depend from independent claim 1 and thus are allowable at least for the reasons herein with respect to claim 1.

New claim 18 recites a smart culture vessel for holding a sample to be tested in a culture medium. It includes a bio-sensor sealed in the vessel in the culture medium with the sample, the bio-sensor having a coating for attracting at least one pathogen expected in the sample. A detection circuit is responsive to the bio-sensor for indicating the presence of a pathogen on the bio-sensor and configured to drive the bio-sensor at a predetermined frequency and to instantaneously and continuously detect a shift in frequency due to the attached pathogen. The cited references are not properly combinable, for at least the reasons given above, to teach or

suggest the combination of elements in the applicants' claim 18.

## CONCLUSION

Accordingly, claims 1-18 are in condition for allowance.

Each of Examiner's have been addressed or traversed. Early and favorable action is respectfully requested.

If for any reason this Response is found to be incomplete, or if at any time it appears that a telephone conference with counsel would help advance prosecution, please telephone the undersigned or his associates, collect in Waltham, Massachusetts at (781) 890-5678.

Respectfully submitted,

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